IN THE MATTER OF THE UNITED STATES PATENT APPLICATION SERIAL NO. 10/020,882 IN FAVOUR OF SHELDON WILLIAM TOBE, APPLICANT AND THE INVENTOR OF THE SUBJECT MATTER THEREIN, FILED December 19, 2001.

DECLARATION

I, Sheldon William Tobe, M.D., Staff Nephrologist, Sunnybrook Health Sciences Centre and Associate Professor of Medicine, University of Toronto. DO SOLEMNLY DECLARE AND AFFIRM THE FOLLOWING:

1. I am the same individual who prepared and filed a declaration dated February 8, 2006 in support of this Application No. 10/020,882. I remain a Staff Nephrologist, Sunnybrook Health Sciences Centre in Toronto, Ontario Canada. I am also an Associate Professor of Medicine at the University of Toronto. A copy of my curriculum vitae was attached to my prior Declaration to which the Examiner is referred. I hold a MD from the University of Calgary, Alberta, Canada, as of June 5, 1985 and a B.Sc. (Honours Biochemistry), as of June 1982 from the University of Toronto, Ontario, Canada. As such I believe I am well qualified to comment and provide opinion in these matters.

2. The following paragraphs contain my comments and opinions concerning the United States Patent Office Examiner's Action dated June 6, 2006, attached as **Exhibit A** to this my Declaration, (hereafter referred to as the Action) concerning U.S. Patent Application No. 10/020,882 entitled "STERILE LOW BICARBONATE DIALYSIS CONCENTRATE" (hereafter referred to as the '882 patent application). To further augment my prior declaration I attach hereto as **Exhibit B** to this my Declaration, the laboratory results detailing the work completed to carry out the Examiner's incorrect allegations that Purcell could inherently be diluted to achieve a Normocarb 25 composition.

3. I was asked by Neil H. Hughes, Patent Agent of the firm Ivor M. Hughes, Barristers and Solicitors, Patent and Trade Mark Agents to provide my opinion concerning the position taken by the United States Patent Office Examiner in the Action and his rejection of claims 1, 9, 14, 17-19 and 21 and his objection of claim 10 of the '882 patent application. In particular, I was asked to provide my opinion with respect to the Examiner's allegation that pending claims 1, 9, 14, 17 and 18 are allegedly anticipated by Purcell et al. (US 5,945,449), and that claims 1, 9, 14, 17-19 and

21 are allegedly unpatentable over Martis et al. (WO 96/01118) in view of Purcell et al. As before I have met with our Agent and have instructed him as to what amendments would be appropriate in view of the U.S. Examiner's allegations. The claims in the application have therefore been amended to identify over any of the references cited for the following reasons.

4. In my opinion, the inventions described in amended claims 1, 9-10, 14, 17-19, 21 and 24 in the '882 patent application are not anticipated nor rendered obvious in light of the teachings and disclosures of the above-mentioned prior art. I thus disagree with the conclusions reached by the Examiner in his Action with respect to the '882 patent application. I have described my opinions in my prior declaration to which the Examiner is referred which are augmented herein, with respect to the Examiner's comments and conclusions concerning the teachings of the prior art. All of the contents of my prior declaration are hereby incorporated by reference into this my second declaration in its entirety as if the contents were fully contained herein.

Summary of the Inventions of the '882 Patent Application

5. The '882 patent application discloses a novel sterile calcium-free low bicarbonate dialysis concentrate composition for use in the preparation of a dialysis solution comprising sodium chloride (NaCl), magnesium chloride (MgCl2), and a concentration of sodium bicarbonate (NaHCO3) sufficiently low so as to allow preparation of a sterile dialysis solution having an effective in vivo bicarbonate concentration of 5-27.5 mmol/L.

6. As also described in the '882 patent application, the primary motivation for the development of the novel concentrate was to address problems known to be associated with buffers in general and there conversion to bicarbonate in the liver. The present claim set addresses this issue.

7. The solution of the present claim set involves the development of a novel dialysis concentrate having a bicarbonate level which when currently diluted will result in a dialysis solution having an effective in vivo bicarbonate level in the range of 5 to 27.5 mmol/L and preferably 25.0 ± 2.5 mmol/L to reflect the "normal" level of bicarbonate of 25.0 mmol/L. This concentrate would be used in the preparation of a dialysis solution for patients who have achieved normal bicarbonate levels. If the bicarbonate level rises in the patient then bicarbonate would pass from the blood to the dialysate, and vice versa. The concentrate also provides, when diluted, the ability to compensate for the conversion of any weak acid, used as an anticoagulant in the dialysis process,

to bicarbonate in the liver and assists in maintaining normal levels or as near to normal levels as possible.

8. U.S. Patent No. 5,945,449 to Purcell et al hereinafter referred to as Purcell was attached to my first declaration. Claims 1, 9, 14, 17 and 18 stand rejected by the Examiner as being allegedly anticipated by Purcell et al (US 5,945,449) dated August 1999. I believe the Examiner is of the mind that Purcell teaches a concentrate which is able to be simply diluted to achieve a sodium of 140. As found at column 6 of Purcell at line 10 it states that the bicarbonate concentrate may be used to produce a dialysis solution by mixing a sterile physiological acceptable diluent with a concentrate. Purcell goes on to specify which diluents are used. At line 20 in column 6 of Purcell the bicarbonate solution is generally prepared by mixing 80 ± 1 ml preferably 80 ml of concentrate with 1L of a sterile physiologically acceptable diluent. When diluted properly one is expected to end up with a solution measured in mmol/L of sodium of 140 ± 14, magnesium of 0.75 ± 0.07, chloride of 106.5 ± 10 and a bicarbonate of 35.0 ± 3.5 providing a 10 percent leeway for each component in either direction. I think Purcell was pretty specific saying that the concentrate should be diluted exactly as describe without going more than 10 percent in either direction. Of course, one could dilute Purcell further to get the bicarbonate concentration down below 30, however, all the other electrolytes would be diluted as well. So if the original NORMOCARB® 35 taught in Purcell is diluted to generate a bicarbonate of 25, the final solution would be 71.43 percent of the original which would dilute the sodium content from 140 to 100 and the chloride content from 106.5 to 76.1. The resulting dialysis solution would not be safe for use and will likely result in the quick death of a patient. Diluting the concentrate to achieve a dialysis solution in this manner is not acceptable. The Examiner has said that the Purcell concentrate is inherently capable of being so diluted. Certainly it is capable of being diluted but I hope that a physician who would try to carry out such a method would have their medical insurance paid in full as they would certainly lose it quickly when carrying out the Examiner's alleged procedure. As stated above in order to further support my comments above, I attach to this my declaration as Exhibit B test results carried out by a laboratory of Apotex Inc. which clearly shows that a direct dilution is not possible to arrive at the present invention and further that the corrections required to adjust the diluted Normocarb 35 is clearly not a simple process. The resulting dialysate volume of 4.6 litres is completely unacceptable for any meaningful use for continuous dialysis. This procedure certainly is not simple and beyond reasonable for the clinical setting.

As supported by the evidence provided herewith as Exhibit B the calculations for the concentration of solutes to put into a diluent to dilute Normocarb 35 concentrate from 25 was complex **and required a degree of complexity greater than** what was required to create the normocarb 35 solution in the first place. In fact the "special dilution solution" would effectively constitute a new invention.

The concentration of ions in the Normocarb 35 concentrate is sodium 1890 mmol/L, Cl 1437.75 mmol/L, HCO3 472.5 mmol/L and Mg 10.125 mmol/L. The number of mmol in 240 ml of Normocarb 35 concentrate is therefore Na 453.6 mmol, Cl 345.06 mmol, HCO3 113.4 mmol and Mg 2.43 mmol.

Therefore as shown in Exhibit B to dilute 113.4 mmol of bicarbonate in 240 ml of concentrate down to 25 mmol/L, with a solution that contains no bicarbonate, requires a final volume of 4.536 L, prepared by adding 4.296 L to the 240 ml of concentrate. This is clearly excessive and not clinically acceptable.

According to my instructions and calculations confirmed by the Apotex laboratory report, to make the desired composition namely in mmol: Na 635.04, Cl 528.444, HCO3 113.4 and Mg 3.402 must be added which is the excess ions required to make up the difference between the required levels and that provided by the diluted Normocarb 35 concentrate in mmol: Na 181.44, Cl 183.384, HCO3 0, Mg 0.972.

The concentration of these ions required in mmol/L in the 4.296L diluent would therefore be in mmol/L: Na 42.2346, Cl 42.687, Mg 0.2262. The salts required would be 42.2346 mmol/L NaCl and 0.2262 mmol/L MgCl2. Given the gram molecular weight of NaCl is 0.05844 gm/mmol and for MgCl2.6h20 is 0.203 gm/mol the following amount of these salts are needed to add to 1L of solution; 2.468 gm of NaCl and 0.045998 gm of MgCl2.6h20.

Further to take 240 ml of Normocarb 35 and attempt to prepare Normocarb 25 requires a larger container to accommodate the solution than is commercially available i.e. available bags are 1L, 2L, 3L and 5L. No commercially prepared diluent to adjust the ion concentrations would be possible. This would also be unacceptable in the clinical realm. Clearly the Examiner's allegation that Purcell could inherently be diluted is incorrect. As stated above the dilution

solution is complex to prepare and would therefore be beyond reason for commercial and clinical application.

9. PCT Patent Publication No. WO 96/01118 to Martis et al. hereinafter referred to as Martis was also affixed to my first declaration and the Examiner is referred to that submission and my comments therein which are herein incorporated by reference. Traditionally peritoneal dialysis solution has always been based on lactate. Lactate that diffuses into the bloodstream is converted into bicarbonate by the liver. Thus every milliequivalent of lactate in the peritoneal dialysis solution is converted into bicarbonate after absorption. This is the reason that a peritoneal dialysis solution has higher levels of bicarbonate equivalents than a hemodialysis solution. A typical peritoneal dialysis lactate is 40 mEq/L.

10. The Martis paper describes a method of adding sodium bicarbonate at a minimum of 20 mmol per liter up to a maximum of 30 mmol/L. It is critical to note that at every instance there is at least an additional 10 mEq of weak acid that is added to the bicarbonate. Thus the solution described by Martis has no less than 30 mEq/L. of bicarbonate and equivalents.

11. NORMOCARB® 25 was designed for patient's who have reached normal levels of bicarbonate. The principle of maintaining a bicarbonate level around the normal physiologic level of 25 mmol/L is an important principle. If the body's bicarbonate level rises above 25 mmol/L, bicarbonate will diffuse into dialysate. If the body's bicarbonate level drifts below 25 mmol/L, bicarbonate will be added to it from the dialysate. This principle is no different for bicarbonate as it is for sodium, chloride or magnesium, the other components of NORMOCARB® 25. During dialysis if the patient's sodium level is above 140, sodium ions will be lost into the dialysate until the level falls to 140. If the sodium level is below 140 sodium ions will enter the bloodstream from the dialysate to rectify the levels. What is novel and inventive about NORMOCARB® 25 is that it is the first dialysis solution to attempt to achieve a normal level of bicarbonate in continuous renal replacement therapy using a "normal" level of bicarbonate in the dialysate.

The Examiner alleges that one skilled in the art would use the Martis dialysis solution in combination with the teachings of Purcell to render the amended patent claims obvious. Again, neither Purcell nor Martis teach an effective in vivo bicarbonate level of bicarbonate equivalents below 27.5. The minimum Martis and Purcell bicarbonate equivalent level is 30 and 31.5

respectively but well above Applicant's teaching. In fact neither party appreciated the benefits available in providing a Normocarb® 25 product.

12. The essence of the present invention is particularly summarized at page 7, lines 16-30,

> "... Usage of a low bicarbonate dialysate solution of the invention takes into account the bicarbonate derived from citrate, and as a result the total effective bicarbonate concentration is accounted for and effectively controlled. Thus, metabolic complications are effectively minimized. The low bicarbonate sterile solution of the invention typically contains a bicarbonate concentration within the range of 5-30 mmol/L, preferably between 20-30 mmol/L, and more preferably 25 ± 2.5 mmol/L. The solutions with bicarbonate concentrations below 25 mmol/L may have sodium citrate added to them up to 20 mmol/L to act as an anticoagulant. *(emphasis added)*
>
> The benefit of such a low concentration of bicarbonate as 25 mmol/L is that if the patients bicarbonate level drops below this, bicarbonate diffuses from the dialysate across the semipermeable membrane to the patient correcting the problem. If there is an excess of bicarbonate in the blood (metabolic alkalosis) then bicarbonate will diffuse out into the dialysate effluent and be removed returning the patient toward normal."

13. Thus, it is my opinion that neither of Purcell or Martis either alone or in any combination thereof teach towards or disclose the claimed inventions as amended in the present submission. As a result, I disagree with the statements made and conclusions reached by the Examiner with respect to these points as described above.

14. I solemnly declare and affirm further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereof.

AFFIRMED before me)
at the Town of Markham)
in the Province of Ontario, Canada)
this 23rd day of November, 2006)

5

Commissioner, Notary Public
for taking Oaths

NEIL HARVEY HUGHES, Notary Public, Province of Ontario, limited to the attestation of instruments and the taking of affidavits, for Ivor M. Hughes, Barrister and Solicitor, Patent and Trademark Agents.
Expires March 30, 2007.

Dr. Sheldon William Tobe, M.D.
Staff Nephrologist, Sunnybrook Health Science Centre
Associate Professor of Medicine, University of Toronto

This is EXHIBIT A referred to in the
Declaration of Sheldon William Tobe, M.D.
sworn this 23rd day of November, 2006

A Commissioner, Notary, etc.

NEIL HARVEY HUGHES, Notary Public, Province of Ontario,
limited to the attestation of instruments and the taking of
affidavits, for Ivor M. Hughes, Barrister and Solicitor,
Patent and Trademark Agents.
Expires March 30, 2007.

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10/020,882	12/19/2001	Sheldon Tobe	PT-1949001	8815

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EXAMINER	
PAK, JOHN D	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 06/06/2006

Sept. 6, 2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/020,882	TOBE, SHELDON	
	Examiner	Art Unit	
	JOHN PAK	1616	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2006 and 15 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21* is/are pending in the application.

4a) Of the above claim(s) *2-8,11-13,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,14,17-19 and 21* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Office action is in response to applicant's remarks and amendment of 3/15/2006 and remarks and declaration of 2/9/2006.

Claims 1-19 and 21 are pending in this application. Pursuant to the restriction requirement and applicant's election of record, claims **1, 9-10, 14, 17-19 and 21** will presently be examined to the extent that they read on the elected subject matter. Claims 2-8, 11-13 and 15-16 remain withdrawn from further consideration as being directed to non-elected subject matter.

Applicant is advised of the following. Claim 18 will be objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1 if and when claim 1 is allowed. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Applicant is requested to cancel claim 18.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in – (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United states before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the

international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 9, 14, 17 and 18 are rejected under 35 USC 102(b) as being anticipated by Purcell et al. (US 5,945,449).

Purcell et al. explicitly disclose a sterile calcium-free bicarbonate concentrate comprising 86.87 ± 8.6 g/l NaCl, 2.05 ± 0.2 g/l $MgCl_2$, and 39.69 ± 3.9 g/l $NaHCO_3$ (column 4, lines 52-56). A sterile, diluted solution is also disclosed, wherein 140 ± 14 mM Na, 0.75 ± 0.07 mM Mg, 106.5 ± 10 mM Cl, and 35 mM ± 3.5 HCO_3 are present (column 4, lines 59-63). The concentrate is used in the field of peritoneal dialysis and hemodialysis (column 4, lines 66-67).

It is clearly recognized by the Examiner that instant claim 1 recites, "concentration of bicarbonate [ ] sufficiently low so as to allow preparation of a sterile dialysis solution for continuous renal replacement therapy having a bicarbonate concentrate of 5-27.5 mmol/l." The claim language in independent claims 14 and 17 is similar in that the concentrate is formulated such that the resulting solution has a bicarbonate level within the range of 5-27.5 mmol/l.

However, it must also be recognized that applicant's claims here are directed either to the concentrate per se or a diluted form without any further specificity as to composition makeup. Even though Purcell et al. did not actually dilute their concentrate so that it resulted in 5-27.5 mM HCO_3, Purcell's concentrate is inherently capable of being so diluted. Any bicarbonate-containing concentrate can allow the diluted form to have 5-30 mM HCO_3. This is a necessary property of the concentrate and it cannot be somehow extinguished by the actual diluted solution obtained by Purcell et al. Therefore, since Purcell's sterile, calcium-free concentrate contains 39.69 ± 3.9 g/l $NaHCO_3$, said concentrate would necessarily have been capable of being diluted to provide a solution that contains 5-30 mM HCO_3.

The claim language pertaining to minimizing risk to metabolic complications and continuous renal replacement therapies (CRRT) such as dialysis and hemofiltration are noted, but since Purcell's composition contains the same composition ingredients or composition ingredients that cannot be distinguished from applicant's claimed composition, and since Purcell's composition is suitable for hemodialysis and peritoneal dialysis, such properties would have been necessarily present in Purcell's composition. MPEP 2112, 2112.01.

All of applicant's claim features are thereby met. The claims are anticipated.

Applicant's arguments filed on 3/15/2006 and arguments and declaration filed on 2/9/2006 have been given due consideration but they were deemed unpersuasive.

Applicant/Declarant overestimates the limiting effect of the claim language in excluding prior art such as Purcell et al. The reference by Purcell et al. is applicable because instant claims are too broadly drafted. No amount of scientific or legal argument can get around this fact.

Applicant seems to be arguing that the claims imply a direct dilution of concentrate → solution. Where is the claim language for that interpretation? Where does it say in any of the claims, "take only the concentrate, don't add anything else except water, and dilute only the concentrate to provide for the final solution." Where in the claims is there prohibition to add additional ingredients to formulate the final solution? It is not uncommon in the dialysis art to combine two or more sources to arrive at a final solution.

1. (currently amended) A sterile calcium free low bicarbonate dialysis concentrate composition for continuous renal replacement therapy for use in the preparation of a dialysis solution comprising sodium chloride (NaCl), magnesium chloride ($MgCl_2$), and a concentration of ~~bicarbonate~~ sodium bicarbonate ($NaHCO_3$) sufficiently low so as to allow preparation of a sterile dialysis solution for continuous renal replacement therapy having a ~~bicarbonate concentrateion of 5-30~~27.5 mmol/l.

Applicant's claim language, as illustrated in claim 1 above, requires that the concentrate is "for" CRRT, "for use in the preparation of a dialysis solution" (does not say for example, "for use with no other added ingredients except water"), and bicarbonate concentration "sufficiently low so as to allow" the preparation of a dialysis solution for CRRT having bicarbonate concentration of 5-27.5 mmol/l.

Here, Purcell's concentrate can be "for" CRRT, can be "for use" in the preparation of a dialysis solution, and can be diluted to provide a bicarbonate concentration of 5-27.5 mmol/l. Purcell's disclosure therefore meets applicant's claim language since it does not preclude addition of other ingredients to arrive at the final solution. It is applicant who chose to claim the concentrate by describing what a prepared solution is to contain, not what the claimed concentrate contains. Applicant has to abide by the consequence of such patent claim drafting strategy.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, 14, 17-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martis et al. (WO 96/01118) in view of Purcell et al.

Martis et al. disclose a peritoneal dialysis solution that comprises:

Dextrose	1.5-4.25 g/dl
Na	100-140 mEq/l
Cl	70-110 mEq/l
Calcium	0.0-4.0 mEq/l
Mg	0.0-4.0 mEq/l
Bicarbonate	20.0-30.0 mEq/l
Weak acid	10-20 mEq/l.

See Martis' claim 7.

Applicant's calcium free feature is met by Martis' clear teaching of 0.0 mEq/l of calcium. Martis' 20-30 mEq/l bicarbonate concentration is expressly within applicant's concentration range. A sterile concentrate or solution is not explicitly disclosed by Martis et al. However, one having ordinary skill in the art would have been motivated to provide a sterile dialysis solution in order to ensure patient safety. Applicant's designation of "concentrate" does not provide sufficient distinguishing weight because there is no specific dilution factor claimed. Even if there were a specific dilution factor claimed, one having ordinary skill in the art would have been motivated to first formulate a concentrate and then dilute the concentrate to the component concentration disclosed and suggested by Martis et al., because concentrates provide the advantage of storage stability and convenience.

Further, the patent by Purcell et al. (US 5,945,449) is cited to establish that one having ordinary skill in the art would have been well aware of the benefit

of using a sterile peritoneal dialysis solution, which is obtained from a sterile dialysis concentrate. See from column 4, line 64 to column 5, line 7.

While the composition makeup in Purcell et al. is different, their disclosure establishes that the level of the ordinary skill in this art would have been such that sterile dialysis concentrate and sterile dialysis solution would have been well within the skill of the ordinary skilled artisan.

Consequently, the ordinary skilled artisan would have been motivated to utilize a sterile dialysis concentrate and prepare a sterile dialysis solution in accordance with Martis' disclosure (e.g., claim 7).

Additionally, because Martis' dialysis solution is biochemically balanced to correct metabolic acidosis (page 4, lines 7-10), applicant's feature of minimizing metabolic complication risks is met. As for the feature of "for continuous renal replacement therapies such as dialysis and hemofiltration," the composition makeup of Martis' dialysis solution and the concentrate suggested thereby would be suitable for such therapies.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly suggested by the teachings of the cited references.[1]

Applicant's arguments filed on 3/15/2006 and arguments and declaration filed on 2/9/2006 have been given due consideration but they were deemed unpersuasive.

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[1] It is noted that claim 10 is not included in this ground of rejection. The Examiner believes that picking and choosing both the calcium free feature and magnesium concentration feature (Mg = 0.75 ± 0.07 mmol/l) is not fairly suggested from Martis' disclosure as a whole and Martis' specific disclosure of
0-4 mEq/l calcium and 0-4 mEq/l magnesium.

Applicant argues that Martis' "effective bicarbonate" is higher than 27.5 mmol/l because the weak acids in Martis' solution "will be converted by the liver to bicarbonate as a one to one conversion rate" (page 15 of the 3/15/06 arguments; see also paragraphs 9-12 of the 2/9/2006 declaration). Applicant argues at length about this feature, but applicant should read the claims again. The claims mention nothing about an "effective" bicarbonate level. The claims require bicarbonate concentration of the diluted solution, not the in vivo conversion rate/concentration of all the solution components. The Examiner maintains that Martis' teaching is applicable to applicant's claim language.

Applicant argues further that Martis' peritoneal dialysis teaching is not relevant to the present claim set because the present claim set has been amended to recite dialysis concentrate/solution for continuous renal replacement therapy, "which is an all together different process." Applicant is reminded that the invention here is directed to the composition per se. The Examiner has established that the dialysis solution taught and suggested by Martis et al. contains the same components as applicant's. It is not a requirement for a rejection under section 103 that the prior art teaches or suggests the same composition for identical purpose. As long as there is a suggestion or motivation to arrive at the claimed subject matter, the rejection is proper. In re Kemps, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996).

Applicant argues that Martis' calcium range of 0.0 to 4.0 mEq/L would lead to chronic loss of calcium and would need regular supplementation. Applicant then curiously argues that calcium should be present in Martis' solution, calcium would precipitate when heat sterilized, and hence, Martis' disclosure is not enabling. Applicant's assumptions are flawed. Martis' claim 7 explicitly discloses 0.0 mEq/L calcium. 0.0 is pretty exact. It means no calcium since 0.0 is less

than 0.00000000000001 mEq/L. Martis et al. chose the precise claim language of 0.0 mEq/L calcium and that is how the disclosure would have been understood by the ordinary skilled artisan.

For these reasons, this ground of rejection, which includes newly amended and considered claims 18-19 and 21, must be maintained.

Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable, *subject to a search update at the time of the next Office action*, if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

It is noted for the record that the Examiner has repeatedly and specifically asked applicant about "NORMOCARB." Repeatedly, applicant has been less than informative as to its/their exact content and its/their prior public use, public disclosure and commercial activity. In answer to the Examiner's previous request for information (Office action of 8/11/2005, paragraph bridging pages 12-13), this is what applicant states:

> Lastly the Examiner reminds applicant about his duty to disclose "all information known to be material to patentability" in this application with respect to NORMOCARB® product information. The Examiner is advised that NORMOCARB® owned by the Assignee was marketed originally by the Assignee consistent with the teachings of Purcell and was based on those teachings. Applicant had previously advised the Examiner of this fact.

Let the record show that the Examiner still does not know what types of NORMOCARB products were in existence, in public use, disclosed publicly,

and/or involved in commercial activity before 12/20/1999. The Examiner does not have any other means to compel applicant to answer these questions and leaves such issues for post-allowance, if necessary.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JOHN PAK
PRIMARY EXAMINER
GROUP 1600

This is EXHIBIT B referred to in the
Declaration of Sheldon William Tobe, M.D.
sworn this 23rd day of November, 2006

A Commissioner, Notary, etc.

NEIL HARVEY HUGHES, Notary Public, Province of Ontario,
limited to the attestation of instruments and the taking of
affidavits, for Ivor M. Hughes, Barrister and Solicitor,
Patent and Trademark Agents.
Expires March 30, 2007.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY

Analytical Operations
November 08, 2006

Introduction:

Goal: To prepare Normocarb 25 Dialysis Solution from Normocarb 35 Concentrate (1 vial, 240 mL). The final NC25 Dialysis Solution should have the following composition in mMol/L: Na 140, HCO_3 25, Cl 116.5 and Mg 0.75. The salt concentration of NC35 Concentrate is given below.

	NC35 Concentrate Theoretical concentration		
	(in g/L)	**(in mMol/L)**	**(in mMol/240 mL)**
Sodium	43.45	1890	453.6
Magnesium	0.2463	10.134	2.432
Chloride	50.97	1437.7	345.05
Bicarbonate (HCO_3)	28.83	472.5	113.4

That is to dilute 113.4 mMol of bicarbonate in 240 mL of concentrate down to 25 mMol/L of bicarbonate requires a final volume of 4.536 L (ie: 113.4 ÷ 25 = 4.536). The number of mMol required in 4.536L to make the goal composition is presented below:

	NC25 Dialysis Solution (Volume: 4.536 L)				
	Required concentration (in mMol/L)	**Required amount in 4.536 L (in mMol)**		**Amount from 240 mL of NC35 Concentrate (in mMol)**	**Difference (in mMol)**
Sodium	140	x 4.536	635.0	453.6	181.4
Magnesium	0.75	x 4.536	3.402	2.432	0.97
Chloride	116.5	x 4.536	528.44	345.05	183.39
Bicarbonate (HCO_3)	25	x 4.536	113.4	113.4	0

To make 4.536 L from 0.24 L of NC35 concentrate, 4.296 L must be added. Then the amount of these ions required in the 4.296L diluent would therefore be the difference shown in the table above (in mMol: Na 181.4; Cl 183.39; Mg 0.97). Given that the molecular weight of NaCl is 58.44 g/Mol and $MgCl_2.6H_2O$ is 203.3 g/Mol, the amount of these salts to be dissolved in 4.296 L is calculated below.

181.4 mMol of NaCl = 58.44/1000 x 181.4 = **10.6 g of NaCl**
0.97 mMol of $MgCl_2.6H_2O$ = 203.3/1000 x 0.970 = **0.197 g $MgCl_2.6H_2O$**

183.39 mMol of Chloride = 35.45/1000 x 183.39 = 6.5 g Chloride (6.43 g Chloride comes from NaCl + 0.07 g comes from $MgCl_2.6H_2O$)

Therefore to make a solution of NC25 Dialysis Solution from 0.24L of NC 35 Concentrate requires addition of 4.296 L of a solution of 10.6 g of NaCl and 0.197 g of $MgCl_2.6H_2O$ to give a final volume of 4.536 L.

Laboratory Verification:

In order to verify the calculations provided above and to demonstrate that simple dilution of NC35 Concentrate to a Dialysis Solution having Bicarbonate concentration of 25 mMol/L would not result in the concentration of Sodium, Magnesium and Chloride ions equivalent to a NC25 Dialysis Solution and that addition of Sodium Chloride and Magnesium Chloride salts is necessary, the following three Dialysis Solutions were prepared and analyzed.

A. NC25 Concentrate to NC25 Dialysis Solution (Dilution: 240 mL to 3240 mL)
B. NC35 Concentrate to NC25 Dialysis Solution (Dilution 171.4 mL to 3171.4 mL)
C. NC35 Concentrate + addition of Sodium Chloride and Magnesium Chloride salts solution to prepare NC25 Dialysis Solution (Total volume: 4536 mL)

Results:

In Table A, theoretical calculation and test results for a typical NC25 Dialysis Solution prepared from NC25 Concentrate (Batch# HE9310) are shown. As expected, Sodium, Magnesium and Chloride ion concentrations are in close agreement with the theoretical values.

Table A	**NC25 Concentrate** **Theoretical concentration**	**NC25 Dialysis Solution (Dilution: 240 mL → 3240 mL)** **Theoretical concentration**	**Laboratory Test Result**	
			Result	**% of Theoretical concentration**
Sodium	43.45 g/L	140 mMol/L	139.2 mMol/L	99.4%
Magnesium	0.2463 g/L	0.75 mMol/L	0.756 mMol/L	100.8%
Chloride	55.76 g/L	116.5 mMol/L	115.5 mMol/L	99.1%
Bicarbonate	28.35 g/L ($NaHCO_3$)	25 mMol/L (HCO_3)	Not Applicable	

Theoretical calculation and test results for NC25 Dialysis Solution prepared from NC35 Concentrate (Batch HE9341) are presented below in table B. Although the Sodium, Magnesium and Chloride ion concentrations are in agreement with the theoretically calculated values, certainly they differ from what is expected for a NC25 Dialysis Solution.

Table B	**NC35 Concentrate** **Theoretical concentration**	**NC35 to NC25 Dialysis Solution (Dilution: 171.4 mL → 3171.4 mL)** **Theoretical concentration**	**Laboratory Test Result**	
			Result	**% of Theoretical concentration expected for NC25 Dialysis Solution**
Sodium	43.45 g/L	102.1 mMol/L	102.2 mMol/L	73.0%
Magnesium	0.2463 g/L	0.55 mMol/L	0.552 mMol/L	73.6%
Chloride	50.97 g/L	75.7 mMol/L	75.7 mMol/L	65.0%
Bicarbonate	28.83 g/L (HCO_3)	25 mMol/L (HCO_3)	Not Applicable	

In Table C, theoretical calculation and test results for NC25 Dialysis Solution prepared from NC35 Concentrate (Batch HE9341) with added Sodium Chloride and Magnesium Chloride salts are presented. Sodium, Magnesium and Chloride ion concentrations are in agreement with the theoretically calculated values as well as what is expected for a NC25 Dialysis Solution.

Table C	**240 mL NC35 + (10.605 g NaCl + 0.201 g $MgCl_2.6H_2O$ dissolved in 4296 mL of water)**	**NC25 Dialysis Solution (Total volume: 4536 mL)** **Theoretical concentration**	**Laboratory Test Result**	
			Result	**% of Theoretical concentration expected for NC25 Dialysis Solution**
Sodium	Total: 14.6 g	140 mMol/L	140.9 mMol/L	100.6%
Magnesium	Total: 0.0832 g	0.75 mMol/L	0.748 mMol/L	99.7%
Chloride	Total: 18.736 g	116.5 mMol/L	118.5 mMol/L	101.7%
Bicarbonate (HCO_3)	Total: 6.919 g	25 mMol/L (HCO_3)	Not Applicable	

Lab book references: MK12040026; KY12060004

Conclusion:

The laboratory test results confirms the theoretical calculations and that simple dilution of NC35 Concentrate to a Dialysis Solution having a Bicorbonate concentration of 25 mMol/L would not result in the concentration of Sodium, Magnesium and Chloride ions equivalent to that expected for a NC25 Dialysis Solution and addition of Sodium Chloride and Magnesium Chloride salts solution is necessary.

Prepared by: Ram Muthuramu, Manager, Analytical Development Date: 11/08/2006

Reviewed by: _____ Date: Nov 08, 2006
Michelle Luong, Document Reviewer

Approved by: _____ Date: 11/08/2006
Wan Jiang, Director, Analytical Operations

CANADIAN TRADE-MARK DATA

*** Note Data on trade-marks is shown in the official language in which it was submitted.

The database was last updated on: 2006-11-21

APPLICATION NUMBER:	REGISTRATION NUMBER:
0892316	TMA546482

STATUS:	REGISTERED
FILED:	1998-10-05
FORMALIZED:	1998-10-14
ADVERTISED:	2000-02-23
REGISTERED:	2001-06-12

REGISTRANT:

DIALYSIS SOLUTIONS INC.
380 Elgin Mills Road East
Richmond Hill,
L4C 5H2
ONTARIO

REPRESENTATIVE FOR SERVICE:

JOAN CHIAM
(APOTEX INC.)
150 SIGNET DRIVE
TORONTO
ONTARIO M9L 1T9

TRADE-MARK:

NORMOCARB

INDEX HEADINGS:

NORMOCARB
CARB, NORMO

WARES:

(1) Bicarbonate solution as an infusate and as a dialysate in both acute and chronic renal dialysis.

CLAIMS:

Declaration of Use filed May 11, 2001.

ACTION	DATE	BF	COMMENTS
Filed	05 October 1998		
Created	08 October 1998		

Formalized	14 October 1998		
Search Recorded	16 April 1999		
Examiner's First Report	22 June 1999	22 October 1999	
Approved	25 January 2000		
Translation Requested	25 January 2000	16 February 2000	20000208135358
Translation Received	08 February 2000		
Extracted for Advertisement	09 February 2000		Vol.47 Issue 2365 2000/02/23
Advertised	23 February 2000		Vol.47 Issue 2365
Allowed	11 May 2000		
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Assignment Correspondence Created	16 May 2001	16 November 2001	
Rep for Service Changed	31 May 2001		From: 454 To: 12515 / Voir Preuve au dossier/See evidence on File No. 892316
Agent Changed	31 May 2001		From: 454 To: / Voir Preuve au dossier/See evidence on File No. 892316
Amendment to Registration	04 June 2001		Owner Address Change / Voir Preuve au dossier/See evidence on File No. 892316
Registered	12 June 2001		

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Last updated: 2006-11-21 ▲ Important Notices

United States Patent and Trademark Office

Trademarks > Trademark Electronic Search System(Tess)

TESS was last updated on Thu Nov 23 04:18:19 EST 2006

Record 1 out of 1

Typed Drawing

Word Mark	**NORMOCARB**
Goods and Services	IC 005. US 006 018 044 046 051 052. G & S: INTRAVENOUS REPLACEMENT AND DEVICE DIALYSIS SOLUTION, ADMINISTERED IN INTENSIVE CARE UNIT. FIRST USE: 20010103. FIRST USE IN COMMERCE: 20010103
Mark Drawing Code	(1) TYPED DRAWING
Design Search Code	
Serial Number	75589374
Filing Date	November 16, 1998
Current Filing Basis	1A
Original Filing Basis	1B
Published for Opposition	September 28, 1999
Registration Number	2496670
Registration Date	October 9, 2001
Owner	(REGISTRANT) DIALYSIS SOLUTIONS, INC. CORPORATION CANADA 8400 Jane Street, Suite 200 Vaughan, Ontario CANADA L4K 4L8
Attorney of Record	Robert W. Adams
Type of Mark	TRADEMARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 2 2 2005

Dialysis Solutions, Incorporated
c/o Mr. Kalpesh Shroff
Apotex Corporation
Project Leader – Regulatory Affairs
616 Heathrow Drive
LINCOLNSHIRE IL 60069

Re: K050827
Trade/Device Name: Normocarb™ 25 (Sterile Bicarbonate Renal Dialysis Concentrate)
Regulation Number: 21 CFR §876.5820
Regulation Name: Hemodialysis system and accessories
Regulatory Class: II
Product Code: KPO
Dated: July 20, 2005
Received: July 21, 2005

Dear Mr. Shroff:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at one of the following numbers, based on the regulation number at the top of this letter:

21 CFR 876.xxxx	(Gastroenterology/Renal/Urology)	240-276-0115
21 CFR 884.xxxx	(Obstetrics/Gynecology)	240-276-0115
21 CFR 892.xxxx	(Radiology)	240-276-0120
Other		240-276-0100

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Nancy C. Brogdon

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K050827

Device Name: NORMOCARB™ 25 (Sterile Bicarbonate Renal Dialysis Concentrate)

Indications for Use:

NORMOCARB™ 25 Sterile Bicarbonate Renal Dialysis Concentrate, after dilution, is indicated for use as a dialysate, in Continuous Renal Replacement Therapy (CRRT).

Prescription Use X (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Posted November 13, 2003)

David A. Seppons

(Division Sign-Off)
Division of Reproductive, Abdominal, and Radiological Devices
510(k) Number K050827

Apotex Inc - Richmond Hill **Normocarb™25/35** - *ESSENTIAL PRESCRIBING INFORMATION*
SAP Code: 228784 RA Rev1 **Insert Size:** 6" x 7.75"
Reason for Revision: New strength being submitted in 510K, Revised 08/15/05 to amend per FDA.
Date Prepared: March 22/2005 **Stock:** can be run in either 28lb or 35lb **Luminesence:** No

6"

7.75"

DIALYSIS SOLUTIONS INC.

NORMOCARB™25
NORMOCARB™35
Sterile Bicarbonate Renal Dialysis Concentrate

ESSENTIAL PRESCRIBING INFORMATION
March 2005

THERAPEUTIC CLASSIFICATION
Dialysate Concentrate for Hemodialysis.

DEVICE DESCRIPTION
A clear, sterile, nonpyrogenic, calcium-free bicarbonate renal dialysis concentrate.
Composition:
NORMOCARB™ (Undiluted): NORMOCARB™25 contains 90.73 g/L sodium chloride (NaCl), 2.06 g/L magnesium chloride ($MgCl_2$) and 28.35 g/L sodium bicarbonate ($NaHCO_3$) in water for injection.
NORMOCARB™ (Undiluted): NORMOCARB™35 contains 82.84 g/L sodium chloride (NaCl), 2.06 g/L magnesium chloride ($MgCl_2$) and 39.7 g/L sodium bicarbonate ($NaHCO_3$) in water for injection.
Dialysate Solution [NORMOCARB™ (Diluted)]: The dialysate solution (diluted NORMOCARB™), when prepared as directed, contains the following:

Component	Concentration NORMOCARB™25		Concentration NORMOCARB™35	
	(mMol/L)	(mEq/L)	(mMol/L)	(mEq/L)
Sodium (Na)	140.0	140.0	140.0	140.0
Magnesium (Mg)	0.75	1.5	0.75	1.5
Chloride (Cl)	116.5	116.5	106.5	106.5
Bicarbonate (HCO_3)	25.0	25.0	35.0	35.0
Total Anions	141.5 mEq/L		141.5 mEq/L	
Total Cations	141.5 mEq/L		141.5 mEq/L	

The nominal measured final conductivity of the dialysate solution is 140 mmhos/cm at 25°C.
If required in patients on insulin or with hypoglycemia, 12 mL of D50W may be added to the sterile water when preparing the dialysate to provide a concentration of 10.2 mEq/L of dextrose in the diluted solution.
Potassium chloride may be added by physician's orders, usually up to 4 mEq/L. Calcium chloride [up to 1.25 mMol/L (2.5 mEq/L)] may be added to the diluted solution by physician's orders.

INTENDED USE/INDICATIONS
NORMOCARB™, after dilution, is indicated for use as a diasytate, in Continuous Renal Replacement Therapy (CRRT).
Continuous renal replacement therapy is a dialysis continued 24 hours a day to treat critically ill patients with renal failure. NORMOCARB™ is not approved for infusion. CRRT is usually administered to patients in intensive care who require dialysis and are hemodynamically unstable, or whose liver function is either impaired or at risk of impairment. Patients with liver impairment typically are more challenging to manage and may have high requirements for bicarbonate due to ongoing lactic acidosis. Use of lactate-based solutions for dialysis may not correct metabolic acidosis if the liver cannot metabolize more lactate into bicarbonate. The bicarbonate-free lactate-containing dialysis solution will actually remove some bicarbonate from the patient. In addition to a bicarbonate-based dialysis solution, patients with liver impairment and/or severe metabolic acidosis may require additional intravenous infusions of bicarbonate to maintain their pH within acceptable parameters.
The aims of CRRT are control of fluid balance, control of plasma electrolytes, control of acid-base balance and removal of products of metabolism.

CONTRAINDICATIONS
There are no known contraindications to the use of NORMOCARB™.

WARNINGS AND PRECAUTIONS
NORMOCARB™ IS NOT FOR INFUSION.
After prolonged dialysis there is a risk of hypocalcemia and even the possibility of hypoglycemia. This can be prevented with ongoing nutrition, monitoring and replacement, if necessary.
NORMOCARB™ must be diluted with sterile water before use. DO NOT USE NORMAL SALINE, RINGERS LACTATE OR ANY OTHER DILUENT EXCEPT STERILE WATER.
The patient's hemodynamic fluid, electrolyte and acid-base balance should be monitored throughout the procedure.
Since NORMOCARB™ is potassium- and calcium-free, close monitoring of the patient's potassium and calcium levels must be carried out during CRRT. It is recommended that these levels are followed twice daily or according to local CRRT protocols.
NORMOCARB™ must not be used if a precipitate has been formed or if container seals have been damaged.
NORMOCARB™ should not be used in dialysate proportioning intermittent hemodialysis machines.
Use in Pregnancy:
No information is available on the use of NORMOCARB™ during pregnancy. Administer to pregnant women only if clearly needed and the potential benefit outweighs the potential risk.

ADVERSE EVENTS
The most common complications during hemodialysis are, in descending order of frequency, hypotension (20 - 30%), cramps (5 - 20%), nausea and vomiting (5 - 15%), headache (5%), itching (5%), chest pain (2 - 5%), back pain (2 - 5%), and fever and chills (<1%).
Less common but serious complications observed during hemodialysis include disequilibrium syndrome, hypersensitivity reactions, arrhythmia, cardiac

tamponade, intracranial bleeding, seizures, hemolysis and air embolism.
Healthcare practitioners should also be aware that dialyzer reactions may occur in patients.

DOSAGE AND ADMINISTRATION

NORMOCARB™ MUST BE DILUTED BEFORE USE. For dilution, one 240 mL vial of NORMOCARB™ should be added to 3 L of sterile water to make 3.24 L of dialysate solution. See RECONSTITUTION below for detailed instructions.

Individualization of Treatment:

The volume of dialysate solution (diluted NORMOCARB™) administered will depend upon the fluid balance of the individual patient, the target fluid balance to be achieved, the body weight and the amount of fluid removed from the patient's circulation during the process of dialysis. DOSAGE MUST THEREFORE BE AT THE DISCRETION OF THE PHYSICIAN.

The usual dosage range commonly used is as follows:

Adults: Usual dialysate flow rate is 1000 to 2000 mL/hr or 20 mL/Kg/hr.
Children: Usual dialysate flow rate is 2 L/1.73 m^2/hr.
Elderly: Usual dialysate flow rate as per adults but will depend on the hemodynamic condition of the elderly patient.

For patients requiring dextrose, D50W may be added to the dialysate according to physician's orders (see **RECONSTITUTION** below for detailed instructions).

RECONSTITUTION (Preparation of Dialysate Solution Using NORMOCARB™ and Sterile Water)

Requirements:

- NORMOCARB™, 1 vented IV transfer set, 1 20 G needle
- 3 L of sterile water
- Alcohol swabs

Important Considerations Before Reconstitution:

NORMOCARB™ must be diluted before use with sterile water only -- do not use normal saline, Ringers Lactate or any other diluent. D50W may be added to sterile water, if required by physician's orders, as described in the method below. Do not manufacture more dialysate than can be used in a 24-hour period.

Method:

1) Remove bag of sterile water from outer protective bag and wipe injection port on bag with alcohol swab.
2) Using aseptic technique:
   a) Assemble IV line, needle, and close clamp
   b) Spike vial
   c) Connect needle to bag
3) Using vial hanger, hang vial from IV pole.
4) Open clamp and empty contents of one 240 mL vial into a 3 L bag of sterile water to make 3.24 L of dialysate.
5) **Special Consideration:** For patients requiring dextrose, 12 mL of D50W may also be added to the bag of sterile water, to make 3.25 L of dialysate with a dextrose concentration of 10.2 mEq/L according to physician's orders.
6) Clamp IV line.
7) Fill out required information on accompanying "Medication Added" sticker and apply to bag.
8) Disconnect needle and IV set.
9) Shake to mix by rocking or rolling the bag and contents thoroughly. When diluted, solution contains approximately (mEq/L):

Diluted Solutions	Na	Mg	Cl	HCO_3
Normocarb™35	140	1.5	106.5	35.0
Normocarb™25	140	1.5	116.5	25.0

10) Connect bag to CRRT dialysis circuit and institute dialysis.

COMPATIBILITY

NORMOCARB™ is physically and chemically compatible with a wide variety of diluents. HOWEVER, FOR USE IN DIALYSIS, NORMOCARB™ MUST BE DILUTED WITH STERILE WATER. **DO NOT USE NORMAL SALINE, RINGERS LACTATE OR ANY DILUENT OTHER THAN STERILE WATER.** NORMOCARB™ is compatible with all systems used for CRRT.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with dialysate solutions should not occur if the procedure is carried out correctly and the patient's fluid, electrolyte and acid-base balance are monitored closely. After prolonged dialysis, fluid and electrolyte changes may occur including hypokalemia, volume depletion, hypophosphatemia, hypocalcemia and possibly vitamin and mineral deficiencies. Continued application of dialysis will remove excess fluid. Regular monitoring and appropriate supplementation, including nutritional supplementation, are part of standard continuous renal replacement therapy care.

HOW SUPPLIED

NORMOCARB™ is available as a clear, sterile, nonpyrogenic, calcium-free bicarbonate renal dialysis concentrate in single-use vials of 240 mL.

Storage:

NORMOCARB™ (Undiluted): Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]. Do not freeze. Do not use if a precipitate has formed or if container seals have been damaged.

Dialysate Solution [NORMOCARB™ (Diluted)]: Because bicarbonate is lost through most plastics used to make diluent bags, once prepared, the dialysate solution (diluted NORMOCARB™) should be used within 24 hours. It may be stored at normal room temperature or refrigerated (2° - 30°C). Do not freeze dialysate or expose to excessive heat.

CAUTION: Federal Law restricts this device to sale by, or on the order of, a physician (or properly licensed practitioner).

Manufactured by: Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

228784

PRODUCT NAME: NORMOCARB 25_35
PRODUCT NUMBER: 228784 RA Rev1
PHARMACODE NUMBER: N/A

SPECIFICATIONS

COLORS (FRONT): Black
(BACK): Black
PAPER TYPE AND WEIGHT: Non-Luminescent Stock (28 or 35 lb)
DIMENSIONS – FLAT: 6 in x 7.75 in
FOLDED: N/A
FLAT: 152.4 mm x 196.85 mm
FOLDED: N/A
INSERT: ■
OUTSERT: ☐ GLUE SPOTS: 0
PERF.: N/A
CONFORMITY OF FOLDING: ☐
See Hard Copy For Approvals

INSERT/OUTSERT APPROVAL

Size:_____
Format & Finished Folded Size:_____
Code # Verification:_____
Text Reviewed By:_____
Text Approved By:_____
Comments:_____
_____

PRODUCT NAME: NORMOCARB 25_35
PRODUCT NUMBER: 228784 RA Rev1
PHARMACODE NUMBER: N/A

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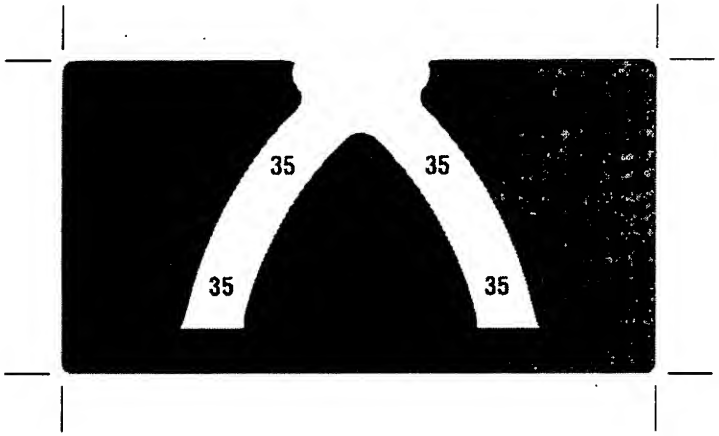
CONFORMITY OF FOLDING: ☐
See Hard Copy For Approvals



APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY - Richmond Hill Site 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
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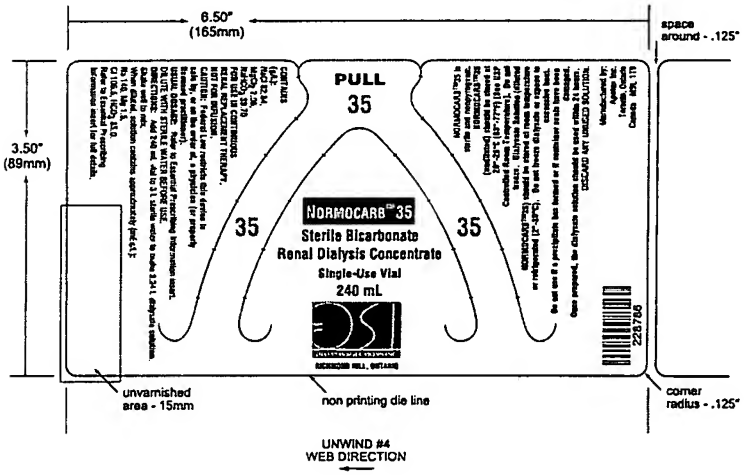
PRINTED PACKAGING MATERIAL PROOF			Copy of	Date March 16, 2005
Material Code 228786	Product Name LBL USA NORMOCARB 35 R/DIAL 240ML			
Previous Code 203675	Label size 89 mm x 165 mm (3.5" x 6.5")			Change Add "35" to label and bold storage conditions.
Colour (s) Black Purple - 520C Fasten Adhesive (back of label) UV Varnish	Web Direction	Printing Flexopress	Paper Stock Satin Litho	
		Caliper 60#	Adhesive Permanent	
Prepared by:		Date:		Reg. Affairs Revision No.: 0



UNWIND #4
WEB DIRECTION

Apotex Inc - Richmond Hill Normocarb™25/35 - *ESSENTIAL PRESCRIBING INFORMATION*
SAP Code: 228784 RA Rev1 Insert Size: 6" x 7.75"
Reason for Revision: New strength being submitted in 510K, Revised 08/15/05 to amend per FDA.
Date Prepared: March 22/2005 Stock: can be run in either 28lb or 35lb Luminescence: No

6"

7.75"

DIALYSIS SOLUTIONS INC.

NORMOCARB™25
NORMOCARB™35
Sterile Bicarbonate Renal Dialysis Concentrate

ESSENTIAL PRESCRIBING INFORMATION
August 2005

THERAPEUTIC CLASSIFICATION
Dialysate Concentrate for Hemodialysis.

DEVICE DESCRIPTION
A clear, sterile, nonpyrogenic, calcium-free bicarbonate renal dialysis concentrate.
Composition:
NORMOCARB™ (Undiluted): NORMOCARB™25 contains 90.73 g/L sodium chloride (NaCl), 2.06 g/L magnesium chloride ($MgCl_2$) and 28.35 g/L sodium bicarbonate ($NaHCO_3$) in water for injection.
NORMOCARB™ (Undiluted): NORMOCARB™35 contains 82.84 g/L sodium chloride (NaCl), 2.06 g/L magnesium chloride ($MgCl_2$) and 39.7 g/L sodium bicarbonate ($NaHCO_3$) in water for injection.
Dialysate Solution [NORMOCARB™ (Diluted)]: The dialysate solution (diluted NORMOCARB™), when prepared as directed, contains the following:

Component	Concentration NORMOCARB™25 (mMol/L)	(mEq/L)	Concentration NORMOCARB™35 (mMol/L)	(mEq/L)
Sodium (Na)	140.0	140.0	140.0	140.0
Magnesium (Mg)	0.75	1.5	0.75	1.5
Chloride (Cl)	116.5	116.5	106.5	106.5
Bicarbonate (HCO_3)	25.0	25.0	35.0	35.0
Total Anions	141.5 mEq/L		141.5 mEq/L	
Total Cations	141.5 mEq/L		141.5 mEq/L	

The nominal measured final conductivity of the dialysate solution is 140 mmhos/cm at 25°C.
If required in patients on insulin or with hypoglycemia, 12 mL of D50W may be added to the sterile water when preparing the dialysate to provide a concentration of 10.2 mEq/L of dextrose in the diluted solution.
Potassium chloride may be added by physician's orders, usually up to 4 mEq/L. Calcium chloride [up to 1.25 mMol/L (2.5 mEq/L)] may be added to the diluted solution by physician's orders.

INTENDED USE/INDICATIONS
NORMOCARB™, after dilution, is indicated for use as a dialysate, in Continuous Renal Replacement Therapy (CRRT).
Continuous renal replacement therapy is a dialysis continued 24 hours a day to treat critically ill patients with renal failure. NORMOCARB™ is not approved for infusion. CRRT is usually administered to patients in intensive care who require dialysis and are hemodynamically unstable, or whose liver function is either impaired or at risk of impairment. Patients with liver impairment typically are more challenging to manage and may have high requirements for bicarbonate due to ongoing lactic acidosis. Use of lactate-based solutions for dialysis may not correct metabolic acidosis if the liver cannot metabolize more lactate into bicarbonate. The bicarbonate-free lactate-containing dialysis solution will actually remove some bicarbonate from the patient. In addition to a bicarbonate-based dialysis solution, patients with liver impairment and/or severe metabolic acidosis may require additional intravenous infusions of bicarbonate to maintain their pH within acceptable parameters.
The aims of CRRT are control of fluid balance, control of plasma electrolytes, control of acid-base balance and removal of products of metabolism.

CONTRAINDICATIONS
There are no known contraindications to the use of NORMOCARB™.

WARNINGS AND PRECAUTIONS
NORMOCARB™ IS NOT FOR INFUSION.
After prolonged dialysis there is a risk of hypocalcemia and even the possibility of hypoglycemia. This can be prevented with ongoing nutrition, monitoring and replacement, if necessary.
NORMOCARB™ must be diluted with sterile water before use. DO NOT USE NORMAL SALINE, RINGERS LACTATE OR ANY OTHER DILUENT EXCEPT STERILE WATER.
The patient's hemodynamic fluid, electrolyte and acid-base balance should be monitored throughout the procedure.
Since NORMOCARB™ is potassium- and calcium-free, close monitoring of the patient's potassium and calcium levels must be carried out during CRRT. It is recommended that these levels are followed twice daily or according to local CRRT protocols.
NORMOCARB™ must not be used if a precipitate has been formed or if container seals have been damaged.
NORMOCARB™ should not be used in dialysate proportioning intermittent hemodialysis machines.
Use in Pregnancy:
No information is available on the use of NORMOCARB™ during pregnancy. Administer to pregnant women only if clearly needed and the potential benefit outweighs the potential risk.

ADVERSE EVENTS
The most common complications during hemodialysis are, in descending order of frequency, hypotension (20 - 30%), cramps (5 - 20%), nausea and vomiting (5 - 15%), headache (5%), itching (5%), chest pain (2 - 5%), back pain (2 - 5%), and fever and chills (<1%).
Less common but serious complications observed during hemodialysis include disequilibrium syndrome, hypersensitivity reactions, arrhythmia, cardiac

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Text Reviewed By:_____
Text Approved By:_____
Comments:_____

tamponade, intracranial bleeding, seizures, hemolysis and air embolism.
Healthcare practitioners should also be aware that dialyzer reactions may occur in patients.

DOSAGE AND ADMINISTRATION

NORMOCARB™ MUST BE DILUTED BEFORE USE. For dilution, one 240 mL vial of NORMOCARB™ should be added to 3 L of sterile water to make 3.24 L of dialysate solution. See RECONSTITUTION below for detailed instructions.

Individualization of Treatment:

The volume of dialysate solution (diluted NORMOCARB™) administered will depend upon the fluid balance of the individual patient, the target fluid balance to be achieved, the body weight and the amount of fluid removed from the patient's circulation during the process of dialysis. DOSAGE MUST THEREFORE BE AT THE DISCRETION OF THE PHYSICIAN.

The usual dosage range commonly used is as follows:

Adults: Usual dialysate flow rate is 1000 to 2000 mL/hr or 20 mL/Kg/hr.
Children: Usual dialysate flow rate is 2 L/1.73 m^2/hr.
Elderly: Usual dialysate flow rate as per adults but will depend on the hemodynamic condition of the elderly patient.

For patients requiring dextrose, D50W may be added to the dialysate according to physician's orders (see **RECONSTITUTION** below for detailed instructions).

RECONSTITUTION (Preparation of Dialysate Solution Using NORMOCARB™ and Sterile Water)

Requirements:

- NORMOCARB™, 1 vented IV transfer set, 1 20 G needle
- 3 L of sterile water
- Alcohol swabs

Important Considerations Before Reconstitution:

NORMOCARB™ must be diluted before use with sterile water only -- do not use normal saline, Ringers Lactate or any other diluent. D50W may be added to sterile water, if required by physician's orders, as described in the method below. Do not manufacture more dialysate than can be used in a 24-hour period.

Method:

1) Remove bag of sterile water from outer protective bag and wipe injection port on bag with alcohol swab.
2) Using aseptic technique:
   a) Assemble IV line, needle, and close clamp
   b) Spike vial
   c) Connect needle to bag
3) Using vial hanger, hang vial from IV pole.
4) Open clamp and empty contents of one 240 mL vial into a 3 L bag of sterile water to make 3.24 L of dialysate.
5) **Special Consideration:** For patients requiring dextrose, 12 mL of D50W may also be added to the bag of sterile water, to make 3.25 L of dialysate with a dextrose concentration of 10.2 mEq/L according to physician's orders.
6) Clamp IV line.
7) Fill out required information on accompanying "Medication Added" sticker and apply to bag.
8) Disconnect needle and IV set.
9) Shake to mix by rocking or rolling the bag and contents thoroughly. When diluted, solution contains approximately (mEq/L):

Diluted Solutions	Na	Mg	Cl	HCO_3
Normocarb™35	140	1.5	106.5	35.0
Normocarb™25	140	1.5	116.5	25.0

10) Connect bag to CRRT dialysis circuit and institute dialysis.

COMPATIBILITY

NORMOCARB™ is physically and chemically compatible with a wide variety of diluents. HOWEVER, FOR USE IN DIALYSIS, NORMOCARB™ MUST BE DILUTED WITH STERILE WATER. **DO NOT USE NORMAL SALINE, RINGERS LACTATE OR ANY DILUENT OTHER THAN STERILE WATER.** NORMOCARB™ is compatible with all systems used for CRRT.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with dialysate solutions should not occur if the procedure is carried out correctly and the patient's fluid, electrolyte and acid-base balance are monitored closely. After prolonged dialysis, fluid and electrolyte changes may occur including hypokalemia, volume depletion, hypophosphatemia, hypocalcemia and possibly vitamin and mineral deficiencies. Continued application of dialysis will remove excess fluid. Regular monitoring and appropriate supplementation, including nutritional supplementation, are part of standard continuous renal replacement therapy care.

HOW SUPPLIED

NORMOCARB™ is available as a clear, sterile, nonpyrogenic, calcium-free bicarbonate renal dialysis concentrate in single-use vials of 240 mL.

Storage:

NORMOCARB™ (Undiluted): Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]. Do not freeze. Do not use if a precipitate has formed or if container seals have been damaged.

Dialysate Solution (NORMOCARB™ (Diluted)): Because bicarbonate is lost through most plastics used to make diluent bags, once prepared, the dialysate solution (diluted NORMOCARB™) should be used within 24 hours. **It may be stored at normal room temperature or refrigerated (2° - 30°C). Do not freeze dialysate or expose to excessive heat.**

CAUTION: Federal Law restricts this device to sale by, or on the order of, a physician (or properly licensed practitioner).

Manufactured by: Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

228784

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY - Richmond Hill Site 380 Elgin Mills R

PRINTED PACKAGING MATERIAL PROOF			
Material Code 228780	Product Name LBL USA NORMOCARB 25 R		
Previous Code N/A	Label size 89 mm x 165 mm (3.5" x 6.5")		
Colour (s) Black Purple - 520C Red - 032C Pattern Adhesive (back of label) UV Varnish	Web Direction Label on OUTSIDE of roll. Copy printed WITH the roll. Left side of label OFF FIRST. PRINTING READS THIS WAY	Printing Flexo Caliper 60#	
Prepared by:		Da